Nebivolol

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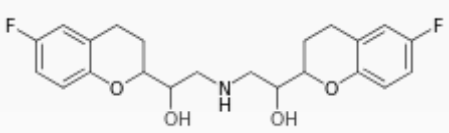

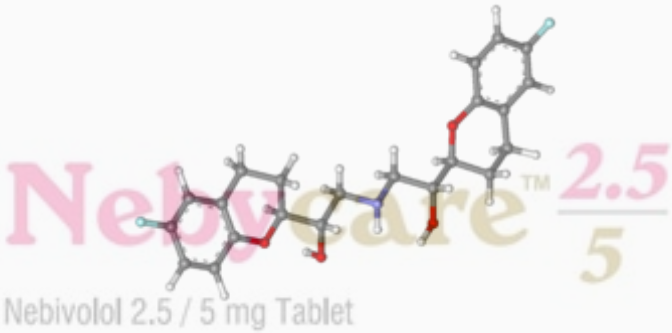

Systematic (IUPAC) name
1-(6-Fluorochroman-2-yl)-{[2-(6-fluorochroman-2-yl)-2-hydroxy-ethyl]amino}ethanol OR 2,2'-Azanediylbis(1-(6-fluorochroman-2-yl)ethanol) OR 1-(6-Fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-{[2-(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-hydroxyethyl]amino}ethan-1-ol

Clinical data	
Trade names	Nebilet, Bystolic
AHFS/Drugs.com	monograph
MedlinePlus	a608029
Licence data	US FDA:link
Pregnancy cat.	C (US)
Legal status	POM (UK) ℞-only (US)

Routes	Oral
Pharmacokinetic data	
Protein binding	98%
Metabolism	Hepatic (CYP2D6-mediated)
Half-life	10 hours
Excretion	Renal and fecal
Identifiers	
CAS number	99200-09-6
ATC code	C07AB12
PubChem	CID 71301
DrugBank	DB04861
ChemSpider	64421
UNII	030Y90569U
KEGG	D05127
ChEMBL	CHEMBL434394
Chemical data	
Formula	$C_{22}H_{25}F_2NO_4$
Mol. mass	405.435 g/mol
SMILES	

- Fc4cc1c(OC(CC1)C(O)CNCC(O)C3Oc2ccc(F)cc2CC3)cc4

InChI

InChI=1S/C22H25F2NO4/c23-15-3-7-19-13(9-15)1-5-21(28-19)17(26)11-25-12-18(27)22-6-2-14-10-16(24)4-8-20(14)29-22/h3-4,7-10,17-18,21-22,25-27H,1-2,5-6,11-12H2

Key:KOHIRBRYDXPAMZ-UHFFFAOYSA-N

Nebivolol is a β_1 receptor blocker with nitric oxide-potentiating vasodilatory effect used in treatment of hypertension and, in Europe, also for left ventricular failure.[1] It is highly cardioselective under certain circumstances.[1]

Pharmacology and biochemistry

β1 Selectivity

Beta blockers help patients with cardiovascular disease by blocking β receptors, while many of the side-effects of these medications are caused by their blockade of β2 receptors.[2] For this reason, beta blockers that selectively block β1 receptors (termed cardioselective or β1-selective beta blockers) produce fewer adverse effects (for instance, bronchoconstriction) than those drugs that non-selectively block both β1 and β2 receptors. Nebivolol has been marketed by Cipla Ltd under brand name Nebicip; by Forest Laboratories under the name Bystolic; by Micro Labs under the brand name Nebilong; ; and by Menarini under the names Hypoloc, Lobivon, Nebilet, Nebilox, Nobiten, and Temerit. In a laboratory experiment conducted on biopsied heart tissue, nebivolol proved to be the most β1-selective of the β-blockers tested, being approximately 3.5 times more β1-selective than bisoprolol.[3] However, the drug's receptor selectivity in humans is more complex and depends on the drug dose and the genetic profile of the patient taking the medication.[4] The drug is highly cardioselective at 5 mg.[5] However, at doses above 10 mg, nebivolol loses its cardioselectivity and blocks both β1 and β2 receptors.[4] (While the recommended starting dose of nebivolol is 5 mg, sufficient control of blood pressure may require doses up to 40 mg).[4] Furthermore, nebivolol is also not cardioselective when taken by patients with a genetic makeup that makes them “poor metabolizers” of nebivolol (and other drugs) or with CYP2D6 inhibitors.[4] As many as 1 in 10 whites and even more blacks are poor CYP2D6 metabolizers and therefore might benefit less from nebivolol's cardioselectivity although currently there are no directly comparable studies.

Vasodilator action

Nebivolol is unique as a beta-blocker.[6] Unlike carvedilol, it has a nitric oxide (NO)-potentiating, vasodilatory effect.[7][8] Along with labetalol, celiprolol and carvedilol, it is one of four beta blockers to cause dilation of blood vessels in addition to effects on the heart.[8] However, recent studies question the clinical relevance of this property to Nebivolol's efficacy.[9]

Antihypertensive effect

Nebivolol lowers blood pressure (BP) by reducing peripheral vascular resistance, and significantly increases stroke volume with preservation of cardiac output.[10] The net hemodynamic effect of nebivolol is the result of a balance between the depressant effects of beta-blockade and an action that maintains cardiac output.[11] Antihypertensive responses were significantly higher with nebivolol than with placebo in trials enrolling patient groups considered representative of the U.S. hypertensive population, in Black patients, and in those receiving concurrent treatment with other antihypertensive drugs.[12]

Pharmacology of side-effect

Several studies have suggested that nebivolol has reduced typical beta-blocker-related side effects, such as fatigue, clinical depression, bradycardia, or impotence.[13][14][15] However, according to the FDA[16]

> Bystolic is associated with a number of serious risks. Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh > B) and in patients who are hypersensitive to any component of the product. Bystolic therapy is also associated with warnings regarding abrupt cessation of therapy, cardiac failure, angina and acute myocardial infarction, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral vascular disease, non-dihydropyridine calcium channel blockers use, as well as precautions regarding use with CYP2D6 inhibitors, impaired renal and hepatic function, and anaphylactic reactions. Finally, Bystolic is associated with other risks as described in the Adverse Reactions section of its PI. For example, a number of treatment-emergent adverse events with an incidence greater than or equal to 1 percent in Bystolic-treated patients and at a higher frequency than placebo-treated patients were identified in clinical studies, including headache, fatigue, and dizziness.

FDA warning letter about advertising claims

In late August 2008, the FDA issued a Warning Letter to Forest Laboratories citing exaggerated and misleading claims in their launch journal ad, in particular over claims of superiority and novelty of action.[16]

Contraindications

- Hepatic insufficiency
- Children
- Pregnancy
- Lactation

Adverse drug reactions

- Headache
- Parasthesia
- Dizziness

History

Mylan Laboratories licensed the U.S. and Canadian rights to nebivolol from Janssen Pharmaceutica N.V. in 2001. Nebivolol is already registered and successfully marketed in more than 50 countries, including the United States where it is marketed under the brand name Bystolic from Mylan Laboratories and Forest Laboratories. Nebivolol is manufactured by Forest Laboratories.

References

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16. ^ [a] [b] Thomas Abrams (2008-08-28). "Warning Letter" (PDF). Food and Drug Administration. Retrieved 2008. "FDA is not aware of any substantial evidence or substantial clinical experience that demonstrates that Bystolic represents a 'novel' or 'next generation' beta blocker for the treatment of hypertension. Indeed, we are not aware of any well-designed trials comparing Bystolic to other β-blockers. Furthermore, FDA is not aware of any data that would render Bystolic's mechanism of action 'unique.'"